Original Article

Nivolumab Treatment Beyond RECIST-Defined Progression in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck in CheckMate 141: A Subgroup Analysis of a Randomized Phase 3 Clinical Trial

Robert Haddad, MD[1]; Fernando Concha-Benavente, MD, PhD[2]; George Blumenschein Jr, MD[3]; Jerome Fayette, MD[4]; Joel Guigay, MD, PhD[5]; A. Dimitrios Colevas, MD[6]; Lisa Licitra, MD[7,8]; Stefan Kasper, MD[9]; Everett E. Vokes, MD[10]; Francis Worden, MD[11]; Nabil F. Saba, MD [12]; Makoto Tahara, MD, PhD[13]; Vijayvel Jayaprakash, MBBS, PhD[14]; Mark Lynch, PhD[14]; Li Li, PhD[14]; Maura L. Gillison, MD, PhD[3]; Kevin J. Harrington, MBBS, PhD[15]; and Robert L. Ferris, MD, PhD [2]

BACKGROUND: Response patterns with immune checkpoint inhibitors may be different from those with chemotherapy. Therefore, assessment of response to immunotherapy with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, could result in premature treatment termination. The randomized, open-label, phase 3 CheckMate 141 trial (NCT02105636), which evaluated nivolumab in recurrent/metastatic squamous cell carcinoma of the head and neck after platinum therapy, allowed treatment beyond first RECIST-defined progression (TBP) according to protocol-specified criteria. **METHODS:** In CheckMate 141, patients with RECIST-defined progression who had a stable performance status and demonstrated clinical benefit without rapid disease progression were permitted to receive TBP with nivolumab at 3 mg/kg every 2 weeks until further progression, which was defined as an additional ≥10% increase in tumor volume. This post hoc analysis evaluated outcomes for patients who received TBP with nivolumab. **RESULTS:** Of 240 patients randomized to nivolumab, 146 experienced RECIST-defined progression. Sixty-two of these patients received TBP, and 84 discontinued treatment (no TBP). Among the 60 TBP patients evaluable for response, 15 (25%) had no change in their tumor burden, and 15 (25%) had reductions in target lesion size; 3 patients (5%) had reductions >30%. The median overall survival among TBP patients was 12.7 months (95% confidence interval, 9.7-14.6 months). No new safety signals were observed with TBP. Exploratory analyses of immune cell biomarkers suggested a potential relationship with initial and TBP responses. **CONCLUSIONS:** Tumor burden reduction was noted in a proportion of patients who received TBP with nivolumab in CheckMate 141. Additional research is warranted to identify factors predictive of a TBP benefit in this population. ***Cancer* 2019;125:3208-3218**.

KEYWORDS: immunotherapy, nivolumab, phase 3 clinical trials, squamous cell carcinoma of the head and neck.

INTRODUCTION

Nivolumab demonstrated a significant overall survival (OS) benefit and a favorable safety profile compared with investigator's choice of therapy in the primary analysis of CheckMate 141 (NCT02105636) in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) who had experienced tumor progression or recurrence within 6 months of platinum-based chemotherapy in the adjuvant, primary (ie, with radiation), recurrent, or metastatic setting.[1] Survival and safety benefits were maintained at the 1- and 2-year follow-up.[2,3]

Corresponding authors: Robert Haddad, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215; robert_haddad@dfci.harvard.edu; Robert L. Ferris, MD, PhD, Hillman Cancer Center Research Pavilion, 5117 Centre Avenue, Suite 2.26b, Pittsburgh, PA 15232; ferrisrl@upmc.edu

[1]Dana-Farber/Harvard Cancer Center, Boston, Massachusetts; [2]Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [3]The University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Centre Leon Berard, Lyon, France; [5]Centre Antoine Lacassagne, FHU OncoAge, Université Côte d'Azur, Nice, France; [6]Stanford University, Stanford, California; [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [8]University of Milan, Milan, Italy; [9]West German Cancer Center, University Hospital, Essen, Germany; [10]University of Chicago Medical Center, Chicago, Illinois; [11]University of Michigan, Ann Arbor, Michigan; [12]Winship Cancer Institute, Emory University, Atlanta, Georgia; [13]National Cancer Center Hospital East, Kashiwa, Japan; [14]Bristol-Myers Squibb, Princeton, New Jersey; [15]National Institute for Health Research Biomedical Research Centre, Royal Marsden/Institute of Cancer Research, London, United Kingdom.

The first and last authors contributed equally to this article.

We thank the patients and their families who made this trial possible and the clinical study teams who participated in the trial; the staff of Dako for the collaborative development of the PD-L1 IHC 28-8 pharmDx assay; and Bristol-Myers Squibb (Princeton, New Jersey) and ONO Pharmaceutical Co, Ltd (Osaka, Japan). Writing and editorial assistance was provided by Meenakshi Subramanian, PhD, CMPP (Evidence Scientific Solutions, Inc), and was funded by Bristol-Myers Squibb. The University of Texas MD Anderson Cancer Center is supported by the National Institutes of Health (grant P30 CA016672).

DOI: 10.1002/cncr.32190, **Received:** December 21, 2018; **Revised:** March 25, 2019; **Accepted:** April 18, 2019, **Published online** June 27, 2019 in Wiley Online Library (wileyonlinelibrary.com)

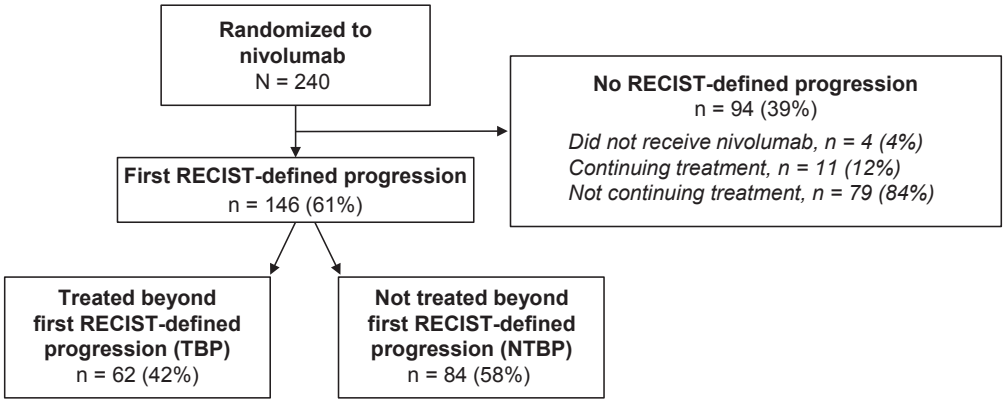


Figure 1. Patient subgroups for the analysis of treatment beyond first RECIST-defined progression. RECIST indicates Response Evaluation Criteria in Solid Tumors.

In CheckMate 141, the tumor response was assessed with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The RECIST guidelines, which were developed for assessment of chemotherapy-treated tumors,[4] assume that early tumor growth indicates progressive disease. With immunotherapy, however, some patients exhibit distinct response patterns, including apparent increases in tumor size due to immune and inflammatory cell infiltration, and/or delayed clinical response.[5] Therefore, RECIST assessment of a tumor response to immunotherapy could result in an incorrect diagnosis of disease progression and premature termination of treatment. In CheckMate 141, treatment beyond first RECIST-defined progression (TBP) with nivolumab was permitted at the discretion of investigators, according to protocol-defined criteria, for patients who were likely to benefit from continued treatment; results from this analysis are reported.

MATERIALS AND METHODS

Patients and Study Design

The full study methodology of the randomized, open-label, phase 3 CheckMate 141 study has been described previously.[1] Patients were randomized 2:1 to receive intravenous nivolumab at 3 mg/kg every 2 weeks or the investigator's choice, which consisted of intravenous methotrexate (40-60 mg/m^2 weekly), docetaxel (30-40 mg/m^2 weekly), or cetuximab (400 mg/m^2 once and then 250 mg/m^2 weekly). Treatment was continued until the occurrence of unacceptable toxicity or disease progression except in patients assigned to the nivolumab treatment arm who met the protocol-defined criteria for TBP. The primary endpoint of the study was OS; patients were followed up for survival during treatment and every 3 months after discontinuation. The objective response rate (ORR), defined as the proportion of patients with a best overall response of confirmed complete response or partial response according to RECIST, version 1.1, was a secondary endpoint. The tumor response was assessed by investigators every 6 weeks beginning week 9. The association of immune cell phenotypes with a clinical response was assessed as an exploratory endpoint. Safety was monitored throughout treatment and for 100 days after the administration of the last dose.

CheckMate 141 was approved by institutional review boards at all participating sites. Patients provided informed consent before enrollment.

Treatment Beyond First RECIST-Defined Progression

Per protocol, TBP was permitted at the discretion of investigators in consultation with the study monitors if a patient demonstrated clinical benefit without rapid disease progression, tolerated nivolumab, maintained a stable performance status, and provided informed consent. Clinical benefit was assessed according to whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment. TBP was not permitted if it would cause a delay in an intervention to prevent serious complications from disease progression. Treatment could continue until evidence of further progression, which was defined as an additional ≥10% increase in the tumor volume from the time of first progression in all target lesions and new measurable lesions.

Patients in the nivolumab arm who received their last dose of treatment after RECIST-defined progression were included in the TBP group; patients whose last dose of nivolumab occurred before RECIST-defined

TABLE 1. Characteristics of Patients With RECIST-Defined Progression Treated With Nivolumab

Baseline Characteristics	TBP Patients (n = 62)	TBP Patients Who Experienced Reductions in Target Lesion Size (n = 15)	NTBP Patients (n = 84)
Age, median (range), y	59.0 (29-78)	58.0 (29-67)	61.0 (30-83)
Male, No. (%)	52 (84)	14 (93)	71 (85)
Primary site of disease, No. (%)			
Oral cavity	26 (42)	3 (20)	33 (39)
Pharynx	28 (45)	9 (60)	36 (43)
Larynx	8 (13)	3 (20)	13 (15)
Other[a]	0	0	2 (2)
Disease sites (primary and metastatic) per patient, No. (%)[b,c]			
1	20 (32)	6 (40)	24 (29)
2	27 (44)	5 (33)	26 (31)
3	8 (13)	2 (13)	27 (32)
≥4	7 (11)	2 (13)	7 (8)
ECOG PS, No. (%)			
0	21 (34)	3 (20)	17 (20)
1	41 (66)	12 (80)	66 (79)
Not reported	0	0	1 (1)
HPV status, No. (%)[d]			
Positive	21 (34)	8 (53)	21 (25)
Negative	19 (31)	4 (27)	17 (20)
Unknown/not reported	22 (35)	3 (20)	46 (55)
PD-L1 expression, No. (%)			
≥1%	27 (44)	5 (33)	28 (33)
<1%	17 (27)	6 (40)	30 (36)
Not quantifiable at baseline	18 (29)	4 (27)	26 (31)
Lactate dehydrogenase			
Median (range), U/L	210.0 (97-1799)[e]	188.0 (114-919)	252.5 (94-4138)
Normal, No. (%)	47 (77)[e]	10 (67)	62 (74)
High, No. (%)	14 (23)[e]	5 (33)	22 (26)
Tobacco use, No. (%)			
Current/former	49 (79)	13 (87)	71 (85)
Never	12 (19)	2 (13)	10 (12)
Unknown	1 (2)	0	3 (4)

Characteristics at First RECIST-Defined Progression	TBP Patients (n = 62)	NTBP Patients (n = 84)
ECOG PS, No. (%)		
0	22 (35)	11 (13)
1	40 (65)	32 (38)
2	0	7 (8)
Not reported	0	34 (40)
Type of RECIST progression, No. (%)		
Target lesion	38 (61)	47 (56)
New lesion	3 (5)	4 (5)
Both	21 (34)	33 (39)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; NTBP, no treatment beyond first RECIST-defined progression; PD-L1, programmed death ligand 1; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.

[a]*Other* includes patients with a tumor in more than 1 of the 3 categories (ie, larynx, oral cavity, and pharynx).

[b]Patients could have had lesions at more than 1 site.

[c]Both target and nontarget lesions are included.

[d]The HPV status was assessed with p16 immunohistochemical testing and was required only for patients with oropharyngeal cancer.

[e]Data were available for 61 patients; percentages were calculated with 61 as the denominator.

progression were included in the no treatment beyond first RECIST-defined progression (NTBP) group.

Biomarkers

Blood samples were collected from patients at baseline and on day 43 of treatment in Vacutainer CPT cell preparation tubes with sodium heparin and were centrifuged according to the manufacturer's recommended procedure to isolate peripheral blood lymphocytes. The cells were washed with phosphate-buffered saline or Roswell Park Memorial Institute 1640 medium and then resuspended in a freezing medium of fetal bovine serum plus 10% dimethyl sulfoxide. The cells were immediately frozen at –70 °C for up to 72 hours before they were moved to long-term storage in liquid nitrogen. Frozen peripheral blood lymphocyte (PBL) samples were

shipped to the analyzing laboratory in liquid nitrogen vapor shippers.

At the laboratory, vials were thawed in a water bath at 37°C for 1 minute; then, the sample from each vial was transferred into a 15-mL conical tube containing warm Roswell Park Memorial Institute 1640 medium, washed twice by sequential centrifugation, resuspended in 5 mL of phosphate-buffered saline and stained with viability dye Zombie Aqua (BioLegend, San Diego, California) according to the manufacturer's protocol, and then stained for multicolor flow cytometry. Samples were stained for $CD8^+$ T cells with the following mouse anti-human monoclonal antibodies: TCRα/β AF700, CD8 APC-Cy7, CCR7-BV650, and CD45RA-BV711. Samples were stained for regulatory T cells with the following mouse anti-human antibodies: CD4-AF700, CD25-BV650, CD127-BV785, and FOXP3-PerCPCy5.5. All antibodies were purchased from BD Bioscience (San Jose, California). Mouse anti-human PD-1-APC (clone MIH4; eBioscience), cytotoxic T lymphocyte antigen 4 (CTLA-4)–PECy5 (clone BNI3; BD Bioscience), and T cell immunoglobulin and mucin-domain containing-3 (TIM-3)–APCCy7 or PE (clone F38-2E2; BioLegend) were also added to $CD8^+$ T cell and regulatory T cell panels with staining performed according to manufacturer protocols. Cells from each sample were analyzed with the BD Fortessa flow cytometer (BD Bioscience, San Diego, California) and FlowJo v10 software (FlowJo, Ashland, Oregon).

Differences in biomarker profiles between TBP patients who had a reduction in target lesions after postprogression nivolumab treatment (TBP responders) and TBP patients who had no change or an increase in target lesions after postprogression treatment (TBP nonresponders) were assessed for association with response to therapy. To serve as control, biomarker assessments were also performed for patients with a RECIST-defined best response of complete or partial response who had not progressed as of the data cutoff (RECIST responders) and for patients with RECIST-defined progressive disease as of the data cutoff (RECIST nonresponders). In addition, immune cell phenotype expression was assessed for similarities between RECIST and TBP responders.

Statistical Analysis

Only patients from the nivolumab arm were included in the TBP analysis of clinical outcomes. OS was estimated with the Kaplan-Meier methodology[6]; 2-sided 95% confidence intervals (CIs) for median OS were computed with a generalization of the Brookmeyer and Crowley method.[7] Two-sided 95% CIs for ORRs were computed with the Clopper and Pearson method.[8] A 2-way analysis of variance with Šidák's multiple comparisons test correction was used to descriptively analyze the PBL biomarker data.[9,10] The database lock for efficacy and safety was September 2016, which represented a minimum follow-up of 11.8 months. The database lock for biomarkers was August 2017.

The Bristol-Myers Squibb policy on data sharing can be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

TABLE 2. Efficacy in the TBP and NTBP Patient Groups Before First RECIST-Defined Progression

	TBP Group (n = 62)	NTBP Group (n = 84)
Best overall response, No. (%)		
Partial response	10 (16)	5 (6)
Stable disease	20 (32)	17 (20)
Progressive disease	32 (52)	62 (74)
Objective response rate, No. (%)	10 (16)	5 (6)
95% CI	8-28	2-13
Maximum reduction in target lesion, median (range), %[a]	7 (−86 to 129)	23 (−85 to 162)
Time to response, median (range), mo[b]	2.1 (1.8-4.8)	2.0 (1.8-5.1)
Duration of response, median (range), mo[b]	6.4 (2.8-9.7)	5.5 (4.0-6.9)

Abbreviations: CI, confidence interval; NTBP, no treatment beyond first RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.
[a]Evaluated for 60 patients in the TBP group and 79 patients in the NTBP group.
[b]For responders (10 in the TBP group and 5 in the NTBP group).

RESULTS

Patients

Of 240 patients randomized to nivolumab, 146 (61%) experienced RECIST-defined progression (Fig. 1). Sixty-two of these patients (42%) met the criteria for TBP and continued to receive nivolumab treatment; 84 (58%) discontinued treatment (NTBP). Among the remaining 94 of 240 patients (39%), 4 did not receive nivolumab, 11 were continuing treatment as of the data cutoff, and the rest discontinued treatment primarily because of either a lack of confirmation of disease progression or adverse events.

Patient characteristics at baseline and at RECIST-defined progression are summarized in Table 1. Overall, the baseline characteristics were similar between patients in the 2 groups, although a larger percentage of TBP patients had a baseline Eastern Cooperative Oncology Group performance status of 0. The most common

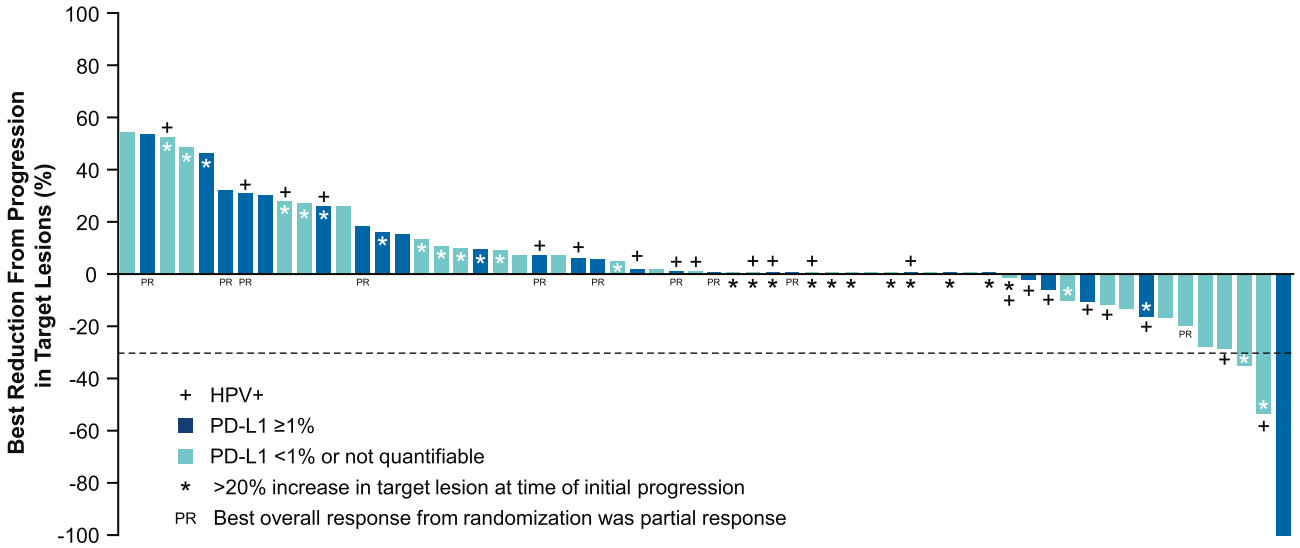


Figure 2. Tumor reduction in patients treated beyond first RECIST-defined progression with nivolumab. HPV indicates human papillomavirus; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

sites of metastases at baseline were similar between the TBP group (lung, 53%; lymph nodes, 48%) and the NTBP group (lung, 52%; lymph nodes, 54%). In both groups, RECIST-defined progression in the majority of patients was due to an increase in the size of target lesions either with (TBP, 34%; NTBP, 39%) or without the development of new lesions (TBP, 61%; NTBP, 56%; Table 1).

Efficacy

The ORR before RECIST-defined progression was higher in the TBP group (16%) than the NTBP group (6%; Table 2). Of the 62 patients who underwent TBP with nivolumab, 60 were evaluable for response; 15 (25%) had no change in their tumor burden, and 15 (25%) had reductions in the target lesion size. Three patients (5%) had a reduction >30% (Fig. 2). For 9 of the 15 patients with reductions in the target lesion size (60%), the pharynx was the primary site of disease (Table 1). Five of the 15 patients with tumor reductions after TBP had previously experienced a >20% increase in the target lesion size at RECIST-defined progression, and only 1 had a preprogression best overall response of partial response. The median time to tumor burden reduction among the 15 patients with reductions after RECIST-defined progression was 3.9 months (range, 3.1-15.8), and the median duration of tumor reduction was 3.0 months (range, <0.1-15.4+). Reductions were observed in patients with human papillomavirus (HPV)-positive and HPV-negative tumors as well as those with tumor programmed death ligand 1 (PD-L1) expression ≥1% or <1%.

Among patients receiving TBP with nivolumab, the median OS was 12.7 months (95% CI, 9.7-14.6 months; Fig. 3A); the estimated OS rates for these patients at 12 and 18 months were 52% and 30%, respectively. In the overall intent-to-treat population (including patients in the TBP and NTBP groups as well as those who did not experience RECIST-defined progression), the median OS for nivolumab-treated patients was 7.7 months (95% CI, 5.7-8.8 months; Fig. 3B).[2] In a landmark analysis, the median OS starting week 6 after RECIST-defined progression was 8.4 months (95% CI, 6.6-10.8 months) in the TBP group and 3.8 months (95% CI, 2.1-5.3 months) in the NTBP group (Fig. 4).

Biomarkers

Peripheral blood lymphocyte samples from baseline and day 43 of treatment were available for 14 TBP patients; 3 of these patients were TBP responders, and 11 were TBP nonresponders. In addition, samples were available for 26 patients assessed with RECIST (16 responders and 10 nonresponders). Across all immune cell phenotypes, there were no significant differences in baseline biomarker levels between RECIST and TBP responders. Differences in the levels of total $CD8^+$ T cells, $PD\text{-}1^+$ $CD8^+$ effector T cells, and exhausted $PD\text{-}1^+$ $TIM\text{-}3^+$ $CD8^+$ effector T cells as well as $PD\text{-}1^+$ regulatory T cells and $CTLA\text{-}4^+$

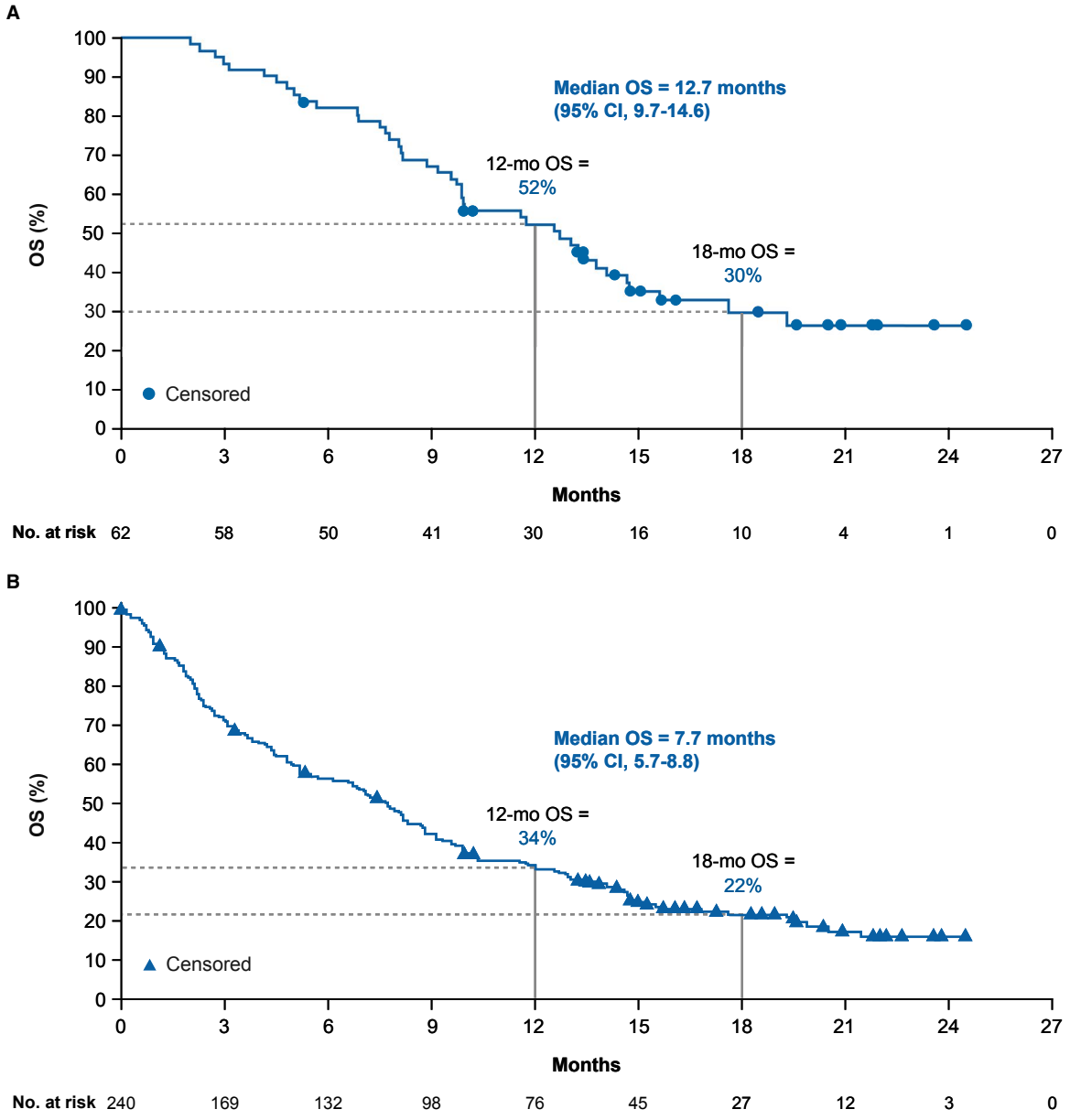


Figure 3. (A) OS in patients treated beyond first RECIST-defined progression with nivolumab. (B) OS in the overall intent-to-treat population of patients (nivolumab arm). CI indicates confidence interval; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors. Reprinted with permission from AlphaMed Press from CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-Line Therapy in Patients with Recurrent/Metastatic Head and Neck Cancer, Gillison, Oncologist 23(9), 2018, permission conveyed through Copyright Clearance Center, Inc.[2]

regulatory T cells were noted between responders and nonresponders (RECIST and/or TBP) at baseline and/or day 43, although not all differences were significant (Fig. 5A,B). There was a wide variation in the levels of CTLA-4$^+$ CD8$^+$ effector T cells. Among TBP responders (n = 3), there was a significant reduction in PD-1$^+$ regulatory T cell levels on day 43 in comparison with baseline; this difference was not noted in nonresponders (n = 11). In contrast, the CD8$^+$ T cell compartment did not show any significant differences between TBP responders and nonresponders after nivolumab treatment.

Safety

Treatment-related adverse events (TRAEs) and select TRAEs are summarized in Table 3. When adjusted for duration of therapy exposure, the incidence of TRAEs, with the exception of skin and subcutaneous tissue disorders, was lower in the TBP group than the NTBP group (Table 4).

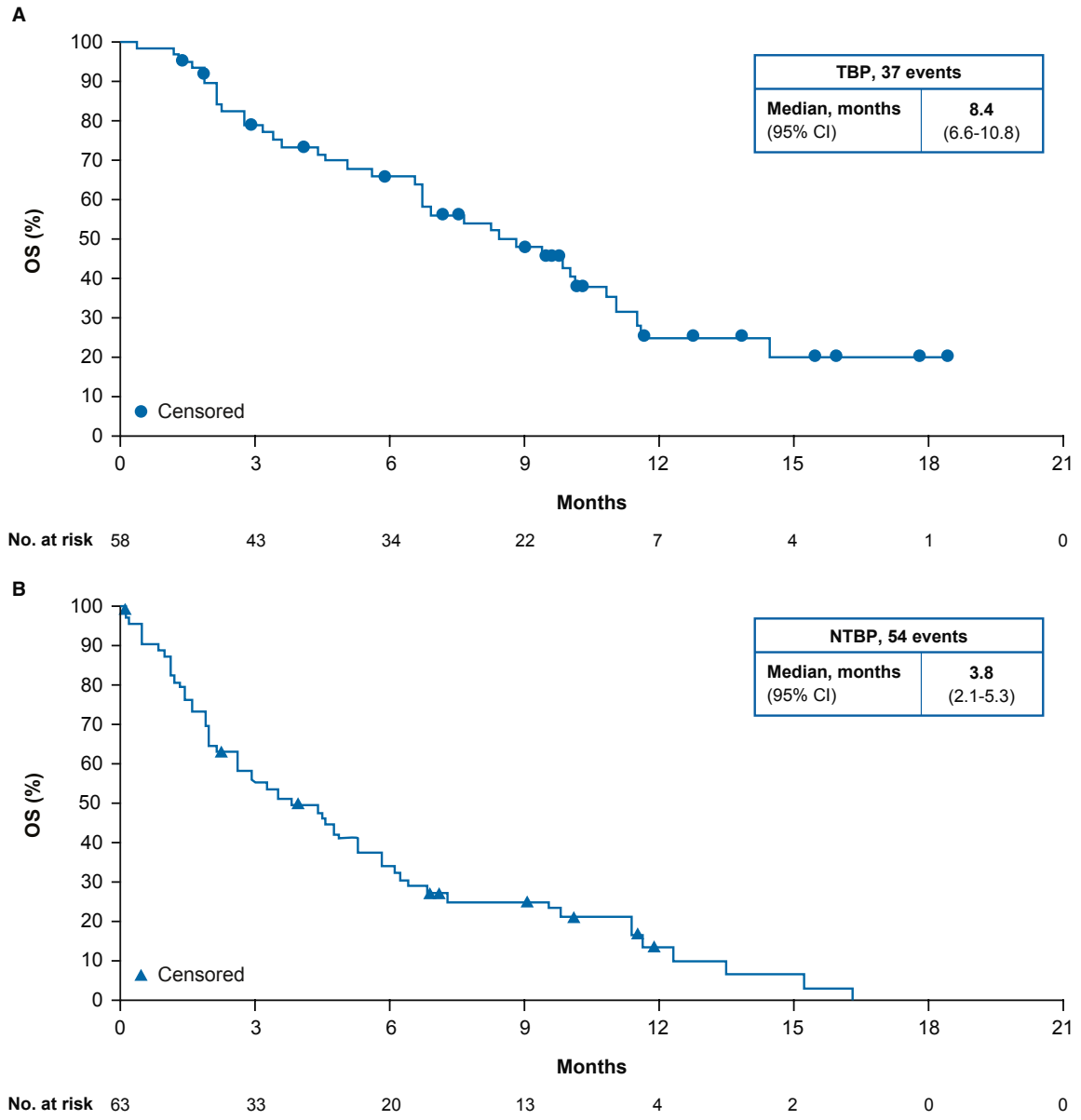
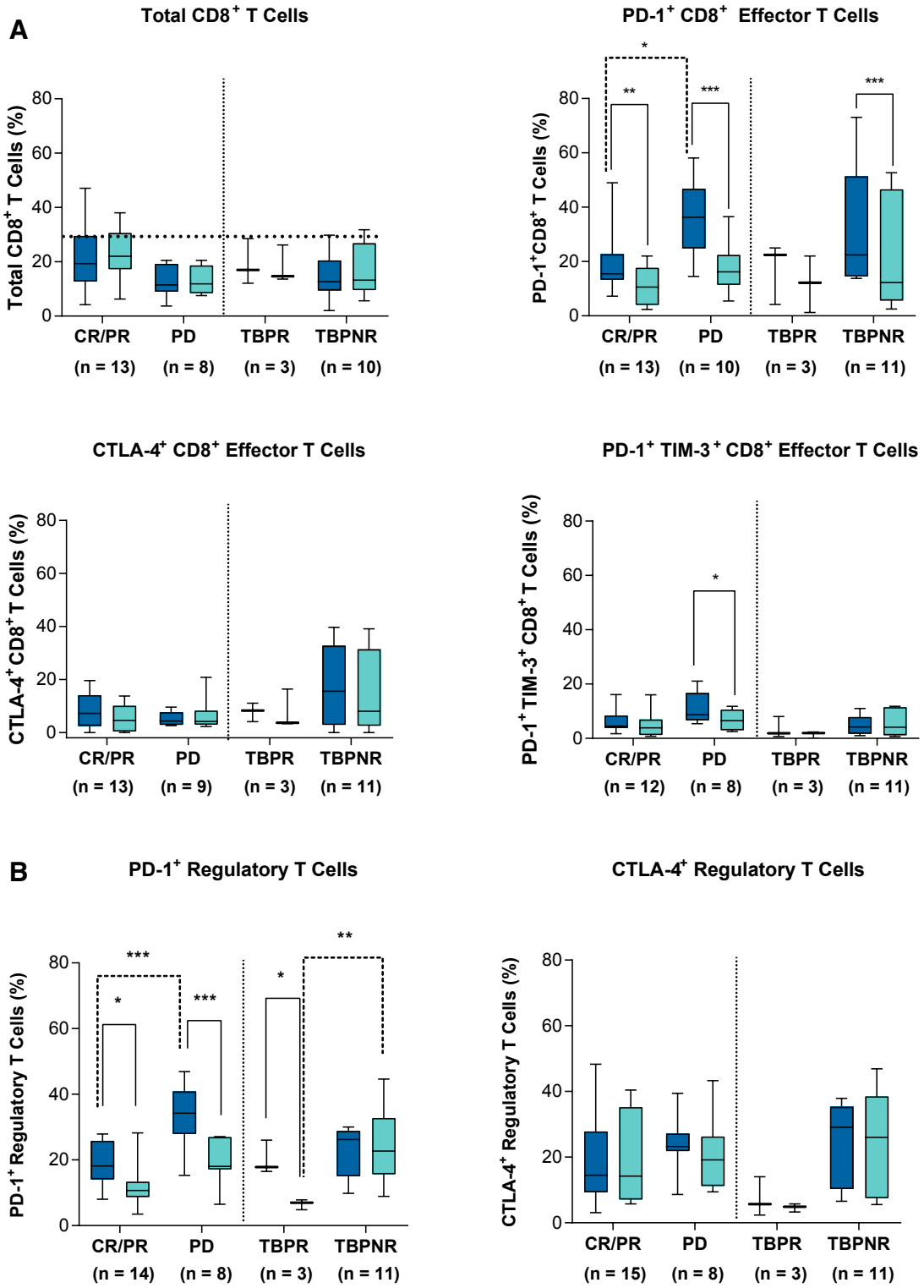


Figure 4. Landmark analysis of OS starting from week 6 after first RECIST-defined progression in (A) the TBP group and (B) the NTBP group. CI indicates confidence interval; NTBP, no treatment beyond first RECIST-defined progression; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.

DISCUSSION

In this post hoc analysis of CheckMate 141, tumor burden reduction was noted in 15 of 60 patients (25%) who underwent TBP with nivolumab; 3 patients (5%) experienced a reduction >30%. In the context of all patients randomized to receive nivolumab in the trial, this translates to an efficacy benefit of treatment beyond progression in 1.3% (3 of 240). The median OS was 12.7 months for patients receiving TBP with nivolumab and 7.7 months in the overall intent-to-treat population.[2] In a landmark analysis, the median OS starting week 6 after RECIST-defined progression was 8.4 months for the TBP group and 3.8 months for the NTBP group. No new safety signals were noted with TBP. Efficacy benefits after TBP with nivolumab have also been reported for melanoma,[11,12] non–small cell lung cancer,[13] and renal cell carcinoma.[14,15]

In CheckMate 141, the ORR before RECIST-defined progression was higher in the TBP group than



the NTBP group; this was expected on the basis of the protocol-defined requirement that patients demonstrate an investigator-assessed clinical benefit to be eligible for TBP. The characteristics of the TBP and NTBP patients were similar at baseline except for a better Eastern Cooperative Oncology Group performance status in the TBP group. These findings are similar to those reported in a recent pooled TBP analysis conducted by the US Food and Drug Administration in patients with melanoma.[12] Among the 15 TBP patients in this analysis who achieved

Figure 5. (A) Levels of $CD8^+$ effector T cells among RECIST-defined responders, RECIST-defined nonresponders, responders to treatment beyond first RECIST-defined progression, and nonresponders to treatment beyond first RECIST-defined progression. (B) Levels of regulatory T cells among the RECIST-defined responders, RECIST-defined nonresponders, responders to treatment beyond first RECIST-defined progression, and nonresponders to treatment beyond first RECIST-defined progression. Dark blue bars represent baseline values; light blue bars represent day 43 values. Horizontal lines indicate medians, boxes indicate interquartile ranges, and whiskers indicate minimum and maximum values. $CD8^+$ effector T cells were defined as $TCR\alpha/\beta^+CD8^+CCR7^-CD45RA^+$. PD-$1^+$ TIM-3^+ $CD8^+$ cells were considered to be exhausted $CD8^+$ effector T cells. Regulatory T cells were defined as $CD4^+CD25^{hi}CD127^{lo}FoxP3^+$. *$P$ < .05; **P < .01; ***P < .001. CR indicates complete response; CTLA-4, cytotoxic T lymphocyte antigen 4; PD, progressive disease; PD-1, programmed cell death 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TBPNR, treatment beyond first RECIST-defined progression with stable or increased tumor lesion after progression; TBPR, treatment beyond first RECIST-defined progression with reduction in tumor lesion after progression; TIM-3, T cell immunoglobulin and mucin-domain containing-3.

TABLE 3. TRAEs Reported in ≥10% of Patients and Select TRAEs

	TBP Patients (n = 62)		NTBP Patients (n = 84)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE, No. (%)	48 (77)	9 (15)	51 (61)	12 (14)
Fatigue	10 (16)	1 (2)	17 (20)	2 (2)
Rash	10 (16)	0	6 (7)	0
Pruritus	9 (15)	0	3 (4)	0
Anemia	3 (5)	1 (2)	9 (11)	2 (2)
Decreased appetite	3 (5)	0	10 (12)	0
Select TRAEs, No. (%)				
Skin	19 (31)	0	10 (12)	0
Endocrine	8 (13)	0	8 (10)	0
Gastrointestinal	6 (10)	0	8 (10)	1 (1)
Hepatic	3 (5)	0	2 (2)	1 (1)
Pulmonary	2 (3)	0	3 (4)	1 (1)
Hypersensitivity/infusion reactions	1 (2)	0	1 (1)	0
Renal	1 (2)	0	0	0

Abbreviations: NTBP, no treatment beyond first RECIST-defined progression; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression; TRAE, treatment-related adverse event.

TABLE 4. Exposure-Adjusted Incidence of Treatment-Related Adverse Events in ≥10% of Patients

	TBP Patients (n = 62)[a]		NTBP Patients (n = 84)[b]	
	Events, No.	Rate per 100 P-Y[c]	Events, No.	Rate per 100 P-Y[c]
Total events	184	489	150	618
Skin and subcutaneous tissue disorders	43	114	13	54
Rash	14	37	6	25
Pruritus	9	24	4	16
General disorders and administration site conditions	26	69	29	119
Fatigue	10	27	18	74
Metabolism and nutrition disorders	17	45	19	78
Decreased appetite	5	13	11	45
Blood and lymphatic system disorders	5	13	12	49
Anemia	3	8	9	37

Abbreviations: NTBP, no treatment beyond first RECIST-defined progression; P-Y, person-years of exposure; RECIST, Response Evaluation Criteria in Solid Tumors; TBP, treatment beyond first RECIST-defined progression.
[a]37.6 P-Y.
[b]24.3 P-Y.
[c]Incidence rate per 100 P-Y = number of events × 100/P-Y.

any reduction in the target lesion size after progression, 8 (53%) had HPV-positive cancers.

It is important to note that although interesting, the small patient numbers in our study preclude us from drawing definitive conclusions about patient characteristics predictive of clinical benefit from treatment with nivolumab beyond RECIST-defined progression. The criteria for TBP used in this analysis are similar to those used for TBP with nivolumab in reports for other tumors. Nonetheless, a key limitation of the analysis is

that the selection of patients for TBP with nivolumab was based on an assessment of clinical benefit by investigators and not on clearly defined, validated factors. Therefore, it is possible that the results of this analysis are confounded by selection bias because patients with more favorable disease characteristics and better prognosis were probably selected for inclusion in the TBP group. Despite the limitations, our analysis underscores the potential benefits of TBP with nivolumab and the need for identifying factors predictive of TBP benefit in this patient population.

Exploratory analyses of cellular immune biomarkers suggested a potential relationship with initial and TBP responses. TBP with nivolumab appeared to diminish immunosuppressive signals from PD-1^{+} regulatory T cells. It should be noted, however, that the sample sizes were small, and this research should be considered hypothesis-generating. Comprehensive analyses involving larger patient populations in prospective clinical trials are warranted to fully understand these effects. In this study, on-treatment PBL samples were collected on day 43 of treatment, a prespecified time point for the collection of on-treatment PBL samples. The timing was based on the assumption that 6 weeks was adequate to evaluate changes in frequencies in the adaptive immune cell compartment in comparison with baseline values and to assess the expression of markers of activation or exhaustion. However, the timing of the PBL sample collection was independent of the timing of the tumor response; this could have resulted in a large variability in on-treatment biomarker levels.

Because of the limitations of RECIST in accurately characterizing tumor responses to immunotherapy, guidelines such as immune-related response criteria (irRC),[5] immune-related RECIST (irRECIST) and immune-modified RECIST (imRECIST),[16-19] and modified RECIST, version 1.1, for immune-based therapeutics (iRECIST)[20] have been developed. The goal of these guidelines is 2-fold: to ensure that treatment is not prematurely terminated for patients with tumor responses to immunotherapy that are different from responses typical of cytotoxic chemotherapy and to ensure that treatment is discontinued in a timely manner in patients with true disease progression because this can affect potential benefits from subsequent lines of treatment.[20]

In summary, patients with RECIST-defined progression who do not experience rapid disease progression, have a stable performance status, and are able to tolerate treatment may derive a clinical benefit from TBP with nivolumab for recurrent/metastatic SCCHN. Our results underscore the importance of conducting prospective trials aimed at evaluating the eligibility and appropriate selection of patients who may derive a benefit from TBP. Additional research is also needed to determine whether a response to TBP can be predicted on the basis of immunologic factors or patient clinical characteristics. Our results indicate that continued TBP with nivolumab is not associated with new safety concerns.

FUNDING SUPPORT

This study was funded by Bristol-Myers Squibb.

CONFLICT OF INTEREST DISCLOSURES

Robert Haddad has received grants from Bristol-Myers Squibb, Merck, Celgene, Kura, Pfizer, and AstraZeneca and has received personal fees from Bristol-Myers Squibb, Merck, Celgene, Pfizer, AstraZeneca, GlaxoSmithKline, Nanobiotix, and Eisai. George Blumenschein, Jr, has received grants from Adaptimmune, AstraZeneca, Bristol-Myers Squibb, Celgene, Exelixis, Genentech, GlaxoSmithKline, Immatics, Immunocore, Incyte, Kite Pharma, Macrogenics, Medimmune, Merck, Novartis, Roche, Torque, and Xcovery and has received personal fees from AbbVie, Adicet, Amgen, Ariad, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Clovis, Genentech, Johnson & Johnson, Maverick Therapeutics, MedImmune, Merck, Novartis, Roche, Virogin Biotech, and Xcovery. Jerome Fayette has received grants from AstraZeneca, Bristol-Myers Squibb and has received other support from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, Innate Pharma, Biogen. Joel Guigay has received grants from GlaxoSmithKline, Bristol-Myers Squibb, and Merck KGaA and has received other support from AstraZeneca, Bristol-Myers Squibb, Innate Pharma, Nanobiotix, and Merck KGaA. A. Dimitrios Colevas reports personal fees from Aduro Biotech, Inc., ATARA Biotherapeutics, Cue Biopharma, Inc., COTA, Inc, KeyQuest Health, LOXO Oncology, Pfizer DSMB, and has received research/grant support from Abbvie, Atara, AstraZeneca, Bristol-Myers Squibb, Cullinan, CellSight Technologies, Inc., Exelixis, Innate Pharma, Tessa Therapeutics, and Threshhold Pharmaceuticals. Lisa Licitra has received grants/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene International, Eisai, Exelixis, Hoffmann–La Roche, IRX Therapeutics, Medpace, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, and Roche; has received honoraria/consultation fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Debiopharm, Doxa Pharma SRL, Eisai, Health & Life SRL, Immuno-Oncology Hub, Incyte Biosciences Italy SRL, Ipsen Innovation, Kura Oncology, Merck Serono, Merck Sharp & Dohme, Nanobiotics SA, Novartis, Roche, and SOBI; and has received other support from Bayer, Bristol-Myers Squibb, Debiopharm, Merck Serono, Merck Sharp & Dohme, and SOBI. Stefan Kasper has received personal fees and other support from Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Eli Lilly, Merck Serono, Merck Sharp & Dohme, and Roche. Everett E. Vokes has received personal fees from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Merck, and Regeneron. Francis Worden has received personal fees from Merck and other support from Bristol-Myers Squibb. Nabil F. Saba has received other support from Merck, Bristol-Myers Squibb, and Lilly. Dr. Saba has received other support from Bristol-Myers Squibb, Lilly, Merck, and Pfizer. Makoto Tahara has received grants from Ono Pharmaceutical, Bristol-Myers Squibb, Eisai, Otsuka, Boehringer Ingelheim, AstraZeneca, Pfizer, Novartis, and NanoCarrier and has received personal fees from Ono Pharmaceutical, Bristol-Myers Squibb, Merck Sharp & Dohme, Bayer, Eisai, Otsuka, AstraZeneca, and Pfizer. Vijayvel Jayaprakash is an employee of Bristol-Myers Squibb and a former employee of AstraZeneca. Mark Lynch is a former employee of Bristol-Myers Squibb. Li Li is an employee of Bristol-Myers Squibb. Maura L. Gillison has received other support from Merck, Bristol-Myers Squibb, Amgen, AstraZeneca, Celgene, and Aspyrian. Kevin J. Harrington has received grants from AstraZeneca and Merck Sharp & Dohme and has received other support

from AstraZeneca, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme, and Pfizer. Robert L. Ferris has received grants/research and clinical trial support from AstraZeneca/MedImmune, Bristol-Myers Squibb, Merck, Tesaro, and VentiRx Pharmaceuticals and has received advisory board/consultation fees from Amgen, AstraZeneca/MedImmune, Bain Capital Life Sciences, Bristol-Myers Squibb, EMD Serono, GlaxoSmithKline, Iovance Biotherapeutics, Lilly, Merck, Numab Therapeutics, Oncorus, Ono Pharmaceuticals, Pfizer, PPD, Regeneron Pharmaceuticals, Tesaro, Torque Therapeutics, and TTMS; he is also supported by the P50 CA097190-14, P30 CA047904-28, and R01 CA206517 grants. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Robert Haddad: Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Fernando Concha-Benavente:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **George Blumenschein, Jr:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Jerome Fayette:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Joel Guigay:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **A. Dimitrios Colevas:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Lisa Licitra:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Stefan Kasper:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Everett E. Vokes:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Francis Worden:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Nabil F. Saba:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Makoto Tahara:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Vijayvel Jayaprakash:** Analysis and interpretation and writing, review, and/or revision of the manuscript. **Mark Lynch:** Conception and design; development of methodology; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Li Li:** Conception and design; development of methodology; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Maura L. Gillison:** Conception and design; development of methodology; acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Kevin J. Harrington:** Acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript. **Robert L. Ferris:** Conception and design; development of methodology; acquisition of data; analysis and interpretation; and writing, review, and/or revision of the manuscript.

REFERENCES

1. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856-1867.
2. Gillison ML, Blumenschein G Jr, Fayette J, et al. CheckMate 141: 1-year update and subgroup analysis of nivolumab as first-line therapy in patients with recurrent/metastatic head and neck cancer. *Oncologist*. 2018;23:1079-1082.
3. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncol*. 2018;81:45-51.
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
5. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
7. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29-41.
8. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404-413.
9. Abdi H. The Bonferroni and Šidák corrections for multiple comparisons. In: Salkind NJ, ed. Encyclopedia of Measurement and Statistics. Thousand Oaks, CA: Sage; 2007:103-107.
10. Sheskin DJ. Handbook of Parametric and Nonparametric Statistical Procedures. 5th ed. Boca Raton, FL: Chapman & Hall/CRC; 2011.
11. Long GV, Weber JS, Larkin J, et al. Nivolumab for patients with advanced melanoma treated beyond progression: analysis of 2 phase 3 clinical trials. *JAMA Oncol*. 2017;3:1511-1519.
12. Beaver JA, Hazarika M, Mulkey F, et al. Patients with melanoma treated with an anti–PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. *Lancet Oncol*. 2018;19:229-239.
13. Kazandjian D, Keegan P, Suzman DL, Pazdur R, Blumenthal GM. Characterization of outcomes in patients with metastatic non–small cell lung cancer treated with programmed cell death protein 1 inhibitors past RECIST version 1.1–defined disease progression in clinical trials. *Semin Oncol*. 2017;44:3-7.
14. Escudier B, Motzer RJ, Sharma P, et al. Treatment beyond progression in patients with advanced renal cell carcinoma treated with nivolumab in CheckMate 025. *Eur Urol*. 2017;72:368-376.
15. George S, Motzer RJ, Hammers HJ, et al. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression: a subgroup analysis of a randomized clinical trial. *JAMA Oncol*. 2016;2:1179-1186.
16. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013;19:3936-3943.
17. Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST [abstract 1070P]. *Ann Oncol*. 2014;25(suppl 4):iv361-iv372.
18. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol*. 2016;34:1510-1517.
19. Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. *J Clin Oncol*. 2018;36:850-858.
20. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18:e143-e152.